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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/747,798	YOO, GEORGE H.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29 and 31-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant application was transferred to Examiner Quang Nguyen, Ph.D., in Art Unit 1633.

A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submissions filed on 11/21/2007 and 01/11/2008 have been entered.

Amended claims 1-29 and 31-33 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 1-15, 18-27 and 33 are rejected under 35 U.S.C. 102(e) as being anticipated by Sethi et al. (US 2004/0214158). ***This is a new ground of rejection.***

Sethi et al already taught a gene therapy method for selectively killing human papillomavirus (HPV) infected epithelial cells, keratinocytes or cells bearing a human papillomavirus (e.g., a cancer cell, high-grade dysplasia such as a cell comprising an intraepithelial neoplasia (IN), high-grade squamous intraepithelial lesions (SIL), oral lesions, laryngeal carcinoma, a cell comprising an anogenital cancer, a metastatic cell, a cell comprising a solid tumor, a cell comprising a wart and the like) by transferring (including topical and/or oral application) a nucleic acid construct comprising any effector gene, including but not limited to a cytotoxin gene, an apoptosis-inducing gene such as p53, p73, Bax, Bad, FADD, a tumor suppressor gene and the like as well as a reporter gene, operably linked to an HPV responsive promoter into the infected cells of a mammal (human or veterinary) (see at least Summary of the Invention, and particularly paragraphs 17, 49, 69-73; Table 1 on page 5; and claims). Sethi et al also disclosed that the nucleic acid construct is in a viral vector such as a retroviral vector, an adenoviral vector, an AAV vector, a herpes viral vector (paragraphs 12, 19) or the nucleic acid construct is in a delivery agent such as a lipid, a liposome, a cationic lipid or a dendrimer (paragraphs 12, 20). Sethi et al further taught that formulations suitable for oral administration can contain an effective amount of the packaged nucleic acid

suspended in diluents, such as water, saline; or capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as liquids, solids, granules or gelatin and for tablet forms further including one or more lactose, sucrose, colorants, flavoring agents and pharmaceutically acceptable carriers (paragraph 103). The packaged nucleic acids alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation (paragraph 104); or in suitable formulations for rectal administration (paragraph 105); or in suitable formulations suitable for parenteral administration containing aqueous and non-aqueous, isotonic sterile injection solutions which can contain anti-oxidants, buffers, bacteriostats (paragraph 106); or in suitable formulations for topical application such as creams, gels, foams, dermal and transdermal patches as well as ointment (paragraphs 107 and 73). With respect to the douche solution of claim 33, it is noted that the intended use is not given any patentable weight and that a douche is simply a jet of liquid applied to a part of the body, and therefore a douche solution is simply liquid.

Accordingly the teachings of Sethi et al meet every limitation of the instant claims. Therefore, the reference anticipates the instant claims.

Amended claims 1-12, 15, 18, 23-28 and 33 are rejected under 35 U.S.C. 102(a) as being anticipated by Clayman, G. (Ref. C95 in the IDS filed 8/16/04) as evidenced by Oda et al. (Carcinogenesis 17(9):2003-2008, 1996), Flaitz et al. (Oral Oncol. 34:448-453, 1998), Hamada et al. (Cancer Res. 56:3047-3054, 1996; Ref. C40; IDS), Liu et al. (Cancer Res. 55:3117-3122, 1995; Ref. C51; IDS) and as evidenced by Recombinant

DNA Advisory Committee (RAC), Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services. ***This is a modified rejection.***

Clayman describes a clinical protocol for treating humans with premalignancies of squamous epithelium in the oral cavity with an adenoviral vector encoding p53 under control of the CMV promoter by intramucosal injection in the area of the lesion, followed by topical application of a mouthwash comprising the same vector (particularly pages 4-6).

Clayman does not mention papilloma virus infection of cells in the lesion or the cells are induced to undergo apoptosis. However, these characteristics are inherent in a substantial fraction of patients being treated in the clinical protocol taught by Clayman as evidenced by the teachings of Oda et al., Flaitz et al., Hamada et al. and Liu et al. Oda et al disclose that up to 90% of oral cancers have been reported to contain HPV DNA (page 2003, col. 2), and Flaitz et al. disclose that about 50% of oral epithelial dysplasias are infected with HPV, and between one-third to one-half of oral squamous cell carcinoma involve HPV infection (page 452). Additionally, Hamada et al disclose that adenovirus-mediated transfer of a wild-type p53 gene induces apoptosis in cervical cancers and up to 90% of cervical cancers are infected with HPV types 16 and 18 (see at least the abstract and col. 1, third paragraph). Liu et al also teach that wild-type p53 adenoviral gene transfer induces apoptosis in squamous cell carcinoma of the Head and Neck (see at least the abstract). Accordingly, one of skill in the art of oral cancer would have been aware that the treatment method of Clayman would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells in a

substantial fraction of the treated patient population; and that the treated HPV infected cells would undergo apoptosis. With respect to the douche solution of claim 33, it is noted that the intended use is not given any patentable weight and that a douche is simply a jet of liquid applied to a part of the body, and therefore a douche solution is simply liquid.

This document is believed to qualify as prior art under 102(a) as evidence that the subject matter was known and used by others before the filing date of the present application. As indicated on pages 10-12, this presentation appears to have been presented to the RAC in a public meeting on 03/08/01.

Amended claims 1-12, 15, 18, 23-28 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Recombinant DNA Advisory Committee (Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services, pages 10-12) as evidenced by Oda et al. (Carcinogenesis 17(9):2003-2008, 1996), Flaitz et al. (Oral Oncol. 34:448-453, 1998), Hamada et al. (Cancer Res. 56:3047-3054, 1996; Ref. C40; IDS), Liu et al. (Cancer Res. 55:3117-3122, 1995; Ref. C51; IDS). ***This is a modified rejection.***

Recombinant DNA Advisory Committee (RAC) describes a clinical protocol for treating humans with premalignancies of squamous epithelium in the oral cavity with an adenoviral vector encoding p53 under control of the CMV promoter by intramucosal injection in the area of the lesion followed by topical application of a mouthwash comprising the same vector (particularly pages 10-11). RAC specifically discloses that

the premalignant process is reversed by inducing apoptosis in the cancer predisposed cells (page 11, top 3 lines).

RAC does not mention papilloma virus infection of cells in the lesion. However, this characteristic is inherent in a substantial fraction of patients that would be the target of the disclosed treatment as evidenced by the teachings of Oda et al. and Flaitz et al. Oda et al disclose that up to 90% of oral cancers have been reported to contain HPV DNA (page 2003, col. 2), and Flaitz et al. disclose that about 50% of oral epithelial dysplasias are infected with HPV, and between one-third to one-half of oral squamous cell carcinoma involve HPV infection (page 452). Additionally, Hamada et al disclose that adenovirus-mediated transfer of a wild-type p53 gene induces apoptosis in cervical cancers and up to 90% of cervical cancers are infected with HPV types 16 and 18 (see at least the abstract and col. 1, third paragraph). Liu et al also teach that wild-type p53 adenoviral gene transfer induces apoptosis in squamous cell carcinoma of the Head and Neck (see at least the abstract). Accordingly, one of skill in the art of oral cancer would have been aware that the treatment method of Clayman described in RAC would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells in a substantial fraction of the treated patient population. With respect to the douche solution of claim 33, it is noted that the intended use is not given any patentable weight and that a douche is simply a jet of liquid applied to a part of the body, and therefore a douche solution is simply liquid.

Amended claims 1-14, 18-29 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Nielsen et al. (US 2001/004420) as evidenced by Oda et al. (Carcinogenesis 17(9):2003-2008, 1996), Flaitz et al. (Oral Oncol. 34:448-453, 1998), Hamada et al. (Cancer Res. 56:3047-3054, 1996; Ref. C40; IDS), Liu et al. (Cancer Res. 55:3117-3122, 1995; Ref. C51; IDS). ***This is a modified rejection.***

Nielsen et al describe the treatment of cancer in general, including cervical cancer and head and neck cancer, by a combination of p53 gene therapy and gemcitamine chemotherapy. The p53 gene can be delivered by non-viral lipid-based plasmid delivery or by delivery in a viral vector based on adenovirus, AAV, retrovirus or vaccinia virus. The p53 coding sequence in the vector may be under control of a constitutive or tumor specific promoter. Nielsen et al. disclose topical delivery of the vector to the location of a tumor, including to the surgical wound resulting from tumor resection. Pharmaceutical compositions comprising the vector include compositions for transmucosal or transdermal delivery for treatment of tumors in the mouth, nasal mucosa, vagina and uterus are disclosed. Disclosed compositions include emulsions (e.g., cream, ointment or salve), aerosols, tablets, lozenges and suppositories. See entire document, especially paragraphs 3-6, 9, 13-16, 22, 29, 38, 64, 76, 83, 88-93, 101-104 and claims 1-10 and 34-35.

Nielsen et al do not mention papilloma virus infection of cells in the lesion or the cells are induced to undergo apoptosis. However, these characteristics are inherent in a substantial fraction of patients being treated in the method taught by Nielsen et al. as evidenced by the teachings of Oda et al., Flaitz et al., Hamada et al. and Liu et al. Oda

et al disclose that up to 90% of oral cancers have been reported to contain HPV DNA (page 2003, col. 2), and Flaitz et al. disclose that about 50% of oral epithelial dysplasias are infected with HPV, and between one-third to one-half of oral squamous cell carcinoma involve HPV infection (page 452). Additionally, Hamada et al disclose that adenovirus-mediated transfer of a wild-type p53 gene induces apoptosis in cervical cancers and up to 90% of cervical cancers are infected with HPV types 16 and 18 (see at least the abstract and col. 1, third paragraph). Liu et al also teach that wild-type p53 adenoviral gene transfer induces apoptosis in squamous cell carcionoma of the Head and Neck (see at least the abstract).

Accordingly, one of skill in the relevant cancer art would have been aware that the treatment method Nielsen et al. would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells in a substantial fraction of a patient population treated for cervical cancer, head and neck cancer; and that the treated HPV infected cells would undergo apoptosis. With respect to the douche solution of claim 33, it is noted that the intended use is not given any patentable weight and that a douche is simply a jet of liquid applied to a part of the body, and therefore a douche solution is simply liquid.

Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicants' arguments related to the above rejections in the Amendment filed on 11/21/07 (pages 7-12), and the Supplemental Amendment filed on 1/11/08 (pages 2-3)

which is based exclusively on the Declaration of Dr. Gary Clayman, have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. Applicant argue basically that not every malignancy or premalignancy of the cervix or oral cavity involves cells that are infected with HPV, and one can not be certain that in the population of individuals of Clayman that at least one individual had a lesion that included papillomavirus-transformed cells. The mere possibility that such a lesion might include HPV infected cells is not sufficient to establish inherent anticipation and occasional results are not inherent. Accordingly, Clayman does not disclose treatment of any lesion that includes papillomavirus-transformed cells or apoptosis of any such cell as a result of p53 treatment. With respect to slide 8, entitled "Special Protocol Testing Summary Pre Treatment", the slide does not clearly establish that HPV-infected lesions were actually treated, the proposed protocol was not actually implemented, a test for HPV of the microdissected lesion was not performed, and that it is possible all results might have been negative for HPV. Furthermore, even if a microdissection was performed showing HPV positive cells, it is not clear from Clayman whether the subject was excluded from the study.

Once again, please note that Oda et al disclose that **up to 90% of oral cancers** have been reported to contain HPV DNA (page 2003, col. 2), and Flaitz et al. disclose that **about 50% of oral epithelial dysplasias are infected with HPV**, and between one-third to one-half of oral squamous cell carcinoma involve HPV infection (page 452). Additionally, Hamada et al disclose that adenovirus-mediated transfer of a wild-type p53

gene induces apoptosis in cervical cancers and **up to 90% of cervical cancers are infected with HPV types 16 and 18** (see at least the abstract and col. 1, third paragraph). Liu et al also teach that wild-type p53 adenoviral gene transfer induces apoptosis in squamous cell carcinoma of the Head and Neck (see at least the abstract). Accordingly, one of skill in the art of oral cancer would have been aware that the treatment method of Clayman would necessarily involve treatment **of hyperplastic lesions that comprise HPV infected cells in a substantial fraction of the treated patient population; and that the treated HPV infected cells would undergo apoptosis**. Therefore, it is not a mere possibility that at least one individual in the treated patient population of Clayman has a lesion comprising papillomavirus-transformed cells. Slide 8 does not indicate and/or suggest that patients that are positive for HPV are specifically excluded from the treatment protocol.

2. Along the same lines of arguments, Applicant argues that RAC does not disclose papillomavirus infection in cells in the lesion or apoptosis of any papillomavirus-infected cell. Similarly, Nielsen fails to expressly or inherently describe each limitation of the claimed invention, namely papilloma virus infection in cells in the lesion or apoptosis of any papillomavirus-infected cell.

Please refer to the Examiner's responses to Applicant's same arguments in preceding paragraph 1. With respect to the teachings of Nielsen et al., please also note that Hamada et al also disclose that adenovirus-mediated transfer of a wild-type p53 gene induces apoptosis in cervical cancers and **up to 90% of cervical cancers are infected with HPV types 16 and 18.**

3. Applicant argues that the Declaration of Dr. Gary Clayman is a support for the novelty and nonobviousness of the claimed invention. In the Declaration, Dr. Clayman declared that he originally planned to determine whether microdissected lesions were infected with human papillomavirus because he hypothesized that HPV infection of cells makes the cells less responsive to gene therapy with p53 because it was known that HPV expresses the E6 and E7 proteins, which can form specific complexes with tumor suppressor gene products, and particularly HPV E6 protein can bind to p53 protein, which promotes the degradation of p53 protein. However, he also declared that microdissection of lesions to assess for HPV status was not performed as part of the protocol and it was not known at the time of the treatment whether any patient was infected with HPV. Therefore, the Declaration of Dr. Clayman supports Applicant's position that the claimed invention is novel over the Clayman powerpoint presentation and the RAC meeting minutes.

Firstly, it is noted that Dr. Gary Clayman's hypothesis that HPV infection of cells makes the cells less responsive to p53 gene therapy **was not found anywhere in any of the cited prior art**. It is further noted that the ability of HPV E6 protein to bind to endogenous p53 to promote endogenous p53 degradation is at least one of the factors responsible for the transformation of HPV-infected cells. However, Hamada et al disclose that **adenovirus-mediated transfer of a wild-type p53 gene induces apoptosis in cervical cancers and up to 90% of cervical cancers are infected with HPV types 16 and 18** (see at least the abstract and col. 1, third paragraph). Liu et al

also teach that **wild-type p53 adenoviral gene transfer induces apoptosis in squamous cell carcinoma of the Head and Neck** (see at least the abstract).

Secondly, the facts still remain that none of the treated patients was tested for HPV in the treatment method of Dr. Clayman. On the evidence provided by Oda et al disclosing that **up to 90% of oral cancers** have been reported to contain HPV DNA (page 2003, col. 2), and Flaitz et al. reporting that **about 50% of oral epithelial dysplasias are infected with HPV, there is more than a possibility that at least one individual in the treated patient population of Clayman has a lesion comprising papillomavirus-transformed cells**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Amended claims 1, 15-17 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Sethi et al. (US 2004/0214158) or Recombinant DNA Advisory Committee (Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services, pages 10-12) as evidenced by Oda et al. (Carcinogenesis 17(9):2003-2008, 1996), Flaitz et al. (Oral Oncol. 34:448-453, 1998), Hamada et al. (Cancer Res. 56:3047-3054, 1996; Ref. C40; IDS), Liu et al. (Cancer Res. 55:3117-3122, 1995; Ref.

C51; IDS) and in view of Zhang et al. (WO 00/29024). ***This contains a new ground of rejection.***

Sethi et al already taught a gene therapy method for selectively killing human papillomavirus (HPV) infected epithelial cells, keratinocytes or cells bearing a human papillomavirus (e.g., a cancer cell, high-grade dysplasia such as a cell comprising an intraepithelial neoplasia (IN), high-grade squamous intraepithelial lesions (SIL), **oral lesions**, laryngeal carcinoma, a cell comprising an anogenital cancer, a metastatic cell, a cell comprising a solid tumor, a cell comprising a wart and the like) by transferring (including topical and/or oral application) a nucleic acid construct comprising any effector gene, including but not limited to a cytotoxin gene, an apoptosis-inducing gene such as p53, p73, Bax, Bad, FADD, a tumor suppressor gene and the like as well as a reporter gene, operably linked to an HPV responsive promoter into the infected cells of a mammal (human or veterinary) (see at least Summary of the Invention, and particularly paragraphs 17, 49, 69-73; Table 1 on page 5; and claims). Sethi et al also disclosed that the nucleic acid construct is in a viral vector such as a retroviral vector, an adenoviral vector, an AAV vector, a herpes viral vector (paragraphs 12, 19) or the nucleic acid construct is in a delivery agent such as a lipid, a liposome, a cationic lipid or a dendrimer (paragraphs 12, 20). Sethi et al further taught that formulations suitable for oral administration can contain an effective amount of the packaged nucleic acid suspended in diluents, such as water, saline; or capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as liquids, solids, granules or gelatin and for tablet forms further including one or more lactose, sucrose, colorants,

flavoring agents and pharmaceutically acceptable carriers (paragraph 103). The packaged nucleic acids alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation (paragraph 104); or in suitable formulations for rectal administration (paragraph 105); or in suitable formulations suitable for parenteral administration containing aqueous and non-aqueous, isotonic sterile injection solutions which can contain anti-oxidants, buffers, bacteriostats (paragraph 106); or in suitable formulations for topical application such as creams, gels, foams, dermal and transdermal patches as well as ointment (paragraphs 107 and 73).

Recombinant DNA Advisory Committee (RAC) describes a clinical protocol for treating humans with premalignancies of squamous epithelium in the oral cavity with an adenoviral vector encoding p53 under control of the CMV promoter by intramucosal injection in the area of the lesion followed by topical application of a mouthwash comprising the same vector (particularly pages 10-11). RAC specifically discloses that the premalignant process is reversed by inducing apoptosis in the cancer predisposed cells (page 11, top 3 lines). RAC does not mention papilloma virus infection of cells in the lesion. However, this characteristic is inherent in a substantial fraction of patients that would be the target of the disclosed treatment as evidenced by the teachings of Oda et al. and Flaitz et al. Oda et al disclose that up to 90% of oral cancers have been reported to contain HPV DNA (page 2003, col. 2), and Flaitz et al. disclose that about 50% of oral epithelial dysplasias are infected with HPV, and between one-third to one-half of oral squamous cell carcinoma involve HPV infection (page 452). Additionally,

Hamada et al disclose that adenovirus-mediated transfer of a wild-type p53 gene induces apoptosis in cervical cancers and up to 90% of cervical cancers are infected with HPV types 16 and 18 (see at least the abstract and col. 1, third paragraph). Liu et al also teach that wild-type p53 adenoviral gene transfer induces apoptosis in squamous cell carcionoma of the Head and Neck (see at least the abstract). Accordingly, one of skill in the art of oral cancer would have been aware that the treatment method of Clayman described in RAC would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells in a substantial fraction of the treated patient population.

Neither Sethi et al. nor Recombinant DNA Advisory Committee (Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services, pages 10-12) specifically describe liquid compositions for oral delivery of the vector (e.g., a mouthwash) further comprising a flavorant to kill HPV infected cells including those in oral lesions or premalignancies of squamous epithelium in the oral cavity, respectively.

However, at the effective filing date of the present application Zhang et al already described pharmaceutical compositions for gene therapy comprising a recombinant adenovirus vector, and taught that compositions for oral delivery such as a mouthwash may include flavoring agents (e.g., peppermint, oil of wintergreen or cherry flavoring)(pages 56-57).

It would have been obvious for an ordinary skilled artisan to modify the teachings of either Sethi et al. or Recombinant DNA Advisory Committee (Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services, pages 10-12) to include a

flavorant such as peppermint, oil of wintergreen or cherry flavoring into liquid compositions for oral delivery of the vector in light of the teachings of Zhang et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the inclusion of flavorants in oral pharmaceutical compositions is routinely done to improve the palatability of the compositions.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of either Sethi et al. or Recombinant DNA Advisory Committee (Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services, pages 10-12) and Zhang et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 11/21/07 (pages 13-14), and the Supplemental Amendment filed on 1/11/08 (pages 2-3) which is based exclusively on the Declaration of Dr. Clayman, have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicant argues basically that there was no *prima facie* case of obviousness because the cited combination of references (RAC as evidenced by Oda and Flaitz)

does not teach or suggest each limitation of the claimed invention for the same reasons set forth in Applicant's arguments for the above 102 rejections. Applicant further notes that the article of Gillison found that HPV was detected in only 25% of its samples of head and neck cancers and that these cancers had distinct biological that clinical features, which is substantially lower than the frequency reported in Oda and Flaitz. Applicant further argues that Zhang fails to provide the missing teaching or suggestion to provide for topical p53 gene therapy of papillomavirus-infected cells because it is only cited as teaching a flavorant.

With respect to the RAC reference, once again refer to the Examiner's responses to Applicant's same arguments for the above 102 rejections. With respect to the findings of Gillison et al that reported HPV was detected in only 25% of its samples of head and neck cancers, it should be noted **that this is the only study** cited by Applicant that shows **a substantial lower frequency of HPV detected in head and neck cancers**. However, at the effective filing date of the present application evidence provided by Oda et al disclosing that **up to 90% of oral cancers** have been reported to contain HPV DNA (page 2003, col. 2), and Flaitz et al. reporting that **about 50% of oral epithelial dysplasias are infected with HPV, and therefore there is more than a possibility that at least one individual in the treated patient population of Clayman in the RAC has a lesion comprising papillomavirus-transformed cells.**

Amended claims 1 and 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sethi et al. (US 2004/0214158) in view of Chiang et al. (US 2002/0051767; IDS). ***This is a new ground of rejection.***

The teachings of Sethi et al were presented above. However, Sethi et al did not teach the step of further subjecting the treated subject to a secondary anti-hyperplastic therapy.

However, at the effective filing date of the present application Chiang et al already taught an improved cancer treatment method comprising a combination of radiation therapy and transduction with a polynucleotide encoding wild type p53, and that such combination treatment provides a more effective treatment than by using p53 gene therapy alone or radiation therapy alone (see at least the abstract).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Sethi et al. by further subjecting the treated patient with a radiation therapy in light of the teachings of Chiang et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Chiang et al taught clearly that combination treatment provides a more effective treatment than by using p53 gene therapy alone or radiation therapy alone.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Sethi et al. and Chiang et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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